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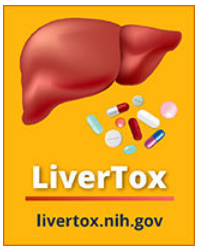


Edaravone

Updated: April 9, 2019.

OVERVIEW

Introduction

Edaravone is a free radical scavenger and neuroprotective agent used for therapy of amyotrophic lateral sclerosis. Edaravone is associated with a low rate of serum aminotransferase elevations during therapy but has not been linked to instances of clinically apparent, acute liver injury.

Background

Edaravone (e dar' a vone) is a free radical scavenger that has been used as a neuroprotective agent in patients with ischemic stroke and amyotrophic lateral sclerosis. The mechanism by which it protects neurons from toxic injury is unknown, but it appears to eliminate lipid peroxide and hydroxyl radicals by electron transfer, thus decreasing oxidative cellular injury which is believed to play an important role in the progressive neurologic damage in amyotrophic lateral sclerosis. Studies in patients with amyotrophic lateral sclerosis suggest that edaravone may slow disease progression and neurologic deterioration. Edaravone was approved for this indication in the United States in 2017 and is increasingly used in management of amyotrophic lateral sclerosis. Edaravone is available in solution for intravenous infusion, generally in single-dose bags of 30 mg/100 mL. The recommended dose is 60 mg given intravenously over 60 minutes for the first 14 days of an initial 28-day cycle, followed by the first 10 days of subsequent cycles. Common side effects include local infusion reactions, confusion, gait disturbance and headache. More severe but uncommon side effects include hypersensitivity reactions including angioedema and anaphylaxis.

Hepatotoxicity

Serum aminotransferase elevations occur in a small proportion of patients on edaravone therapy, but the frequency, timing of onset, duration and severity of these elevations has not been defined. The rates of abnormal liver tests during edaravone therapy were said to be similar to those during placebo treatment. Most elevations resolved spontaneously, and there were no reports of drug discontinuation for serum enzyme elevations. Clinically apparent liver injury due to edaravone was not reported in the prelicensure trials and has not been reported with subsequent clinical use of edaravone, but the numbers of patients treated have been few. Thus, clinically apparent liver injury from edaravone must be rare if it occurs at all.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which edaravone might cause hepatotoxicity is unclear. Edaravone is extensively metabolized by the liver to sulfate and glucuronide conjugates that also demonstrate no toxicity in animal models. Edaravone has not been found to have significant drug-drug interactions.

Outcome and Management

The liver injury arising during edaravone therapy has consisted of minor and transient elevations in serum aminotransferase levels in a small proportion of patients. Routine monitoring of serum aminotransferase levels is not recommended. However, if aminotransferase elevations greater than 5 times ULN are detected during therapy, edaravone should be temporarily discontinued and reinitiated only after resolution of the abnormalities and with close monitoring of liver tests thereafter. Edaravone has not been linked to cases of acute liver failure, chronic hepatitis or vanishing bile duct syndrome.

Drug Class: Alzheimer Disease Agents, Amyotrophic Lateral Sclerosis Agents

Other Related Drugs: Riluzole

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Edaravone – Radicava®

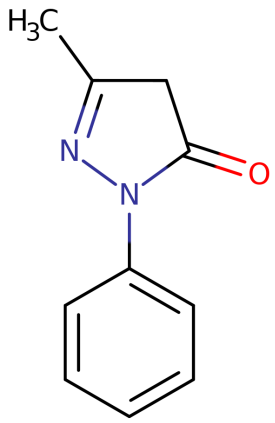
DRUG CLASS

Amyotrophic Lateral Sclerosis Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Edaravone	89-25-8	C10-H10-N2-O	

ANNOTATED BIBLIOGRAPHY

References updated: 09 April 2019

Abbreviations used: ALS, amyotrophic lateral sclerosis

Zimmerman HJ. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 709-42.

(Expert review of hepatotoxicity published in 1999 before the availability of edaravone).

Larrey D. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 2nd ed. New York: Informa Healthcare USA, 2007, pp. 518.

(Review of hepatotoxicity of psychotropic agents published in 2007 before the availability of edaravone).

Roberson ED. Amyotrophic lateral sclerosis (ALT). Treatment of central nervous system degenerative disorders. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 335-7.

(Textbook of pharmacology and therapeutics).

Wokke J. Riluzole. Lancet 1996; 348 (9030): 795-9. PubMed PMID: 8813989.

(Review of structure, mechanisms of action, pharmacokinetics, efficacy and safety of riluzole; mentions that ALT and AST elevations occur not infrequently, but are usually less than 3 times ULN and that no case of jaundice has been reported).

Miller RG, Mitchell JD, Lyon M, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Amyotroph Lateral Scler Other Motor Neuron Disord 2003; 4: 191-206. PubMed PMID: 13129806.

(Systematic review of safety and efficacy of riluzole identified 4 controlled trials; ALT elevations >3 times ULN were 2.6 times more frequent in riluzole than placebo treated subjects).

Yoshino H, Kimura A. Investigation of the therapeutic effects of edaravone, a free radical scavenger, on amyotrophic lateral sclerosis (Phase II study). Amyotrophic Lateral Scler 2006: 7: 247-51.

(Among 20 patients with ALS treated with 30 or 60 mg of edaravone intravenously once daily for 14 days in six 28-day cycles, the rate of worsening of symptom scores decreased in the higher dose group and adverse events were uncommon; "In several cases, laboratory tests showed abnormalities, but none was considered to be a consequence of edaravone administration").

Shinohara Y, Saito I, Kobayashi S, Uchiyama S. Edaravone (radical scavenger) versus sodium ozagrel (antiplatelet agent) in acute noncardioembolic ischemic stroke (EDO trial). Cerebrovasc Dis 2009; 27: 485-92. PubMed PMID: 19321945.

(Among 401 patients with acute ischemic stroke treated with 14 days of intravenous edaravone vs ozagrel, symptom and function scales at 3 suggesting noninferiority while both total and serious adverse event rates were similar including renal, cerebrovascular and hepatic [22% vs 24%], but no details were provided).

Abe K, Itoyama Y, Sobue G, Tsuji S, Aoki M, Doyu M, Hamada C, et al.; Edaravone ALS Study Group. Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients. Amyotroph Lateral Scler Frontotemporal Degener 2014; 15: 610-7. PubMed PMID: 25286015.

(Among 206 patients with ALS treated with 6 cycles of intravenous edaravone or placebo [24 weeks], there were no differences in changes in ALS functional rating scale, disease progression or deaths, and adverse event rates were similar although headache, bruising, gait disturbance and rash were more frequent with edaravone).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 82 [9%] were attributed to central nervous system agents, but none to edaravone, riluzole or other drugs used to treat ALS or Alzheimer disease).

Writing Group; Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well- defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2017; 16: 505-12. PubMed PMID: 28522181.

(Among 137 patients with early stage ALS treated with 6 cycles of intravenous edaravone or placebo [24 weeks], ALS functional rating scores decreased less in the edaravone treated subjects [-5.0 vs -7.5] and adverse event rates were similar including "abnormal liver function tests" which occurred in one patient in both groups).

Writing Group on Behalf of the Edaravone (MCI-186) ALS 19 Study Group. Exploratory double-blind, parallel-group, placebo-controlled extension study of edaravone (MCI-186) in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener 2017; 18 (sup1): 20-31. PubMed PMID: 28872918.

(Among 181 patients with ALS who completed a randomized controlled trial of edaravone [Abe 2014], 93 who had received edaravone were either continued on 6 cycles of active drug or switched to placebo, during which changes in the ALS functional rating scale were similar as were adverse event rates and there were no differences in laboratory measurements between the two groups).

Kalin A, Medina-Paraiso E, Ishizaki K, Kim A, Zhang Y, Saita T, Wasaki M. A safety analysis of edaravone (MCI-186) during the first six cycles (24 weeks) of amyotrophic lateral sclerosis (ALS) therapy from the double-blind period in three randomized, placebo-controlled studies. Amyotroph Lateral Scler Frontotemporal Degener 2017; 18 (sup1): 71-9. PubMed PMID: 28872919.

(Pooled analysis of 3 placebo-controlled trials in 368 patients found some treatment emergent adverse events that occurred more frequently with edaravone were bruising [15% vs 9%], gait disturbance [12.5% vs 9%], headache [8% vs 5%, eczema [6.5% vs 2%] and contact dermatitis [6% vs 3%], while "hepatic function abnormal" arose in 1.2% vs 2.7%).

Writing Group on Behalf of the Edaravone (MCI-186) ALS 19 Study Group. Open-label 24-week extension study of edaravone (MCI-186) in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener 2017; 18 (sup1): 55-63. PubMed PMID: 28872920.

(Among 123 patients with early stage ALS treated in a placebo-controlled trial [Writing Group 2017] who continued in an extension study of edaravone for another 6 cycles [24 weeks], the decline in functional rating scores was linear and no new safety concerns were detected and there were no serious adverse events; no mention of ALT elevations or hepatotoxicity).

Oskarsson B, Gendron TF, Staff NP. Amyotrophic lateral sclerosis: an update for 2018. Mayo Clin Proc 2018; 93: 1617-28. PubMed PMID: 30401437.

(Review of the diagnosis, epidemiology, pathogenesis, clinical features, management and treatment of ALS including discussion of edaravone).